## REMARKS

### 1. Disposition of Claims

Claims 1-24 are pending in this application. Claims 1, 3-7, 9-15 and 21-24 are withdrawn from consideration. Claims 2, 8 and 16-20 are under examination. No new matter has been added. Reexamination and reconsideration of the application, as amended, are respectfully requested.

### 2. Compliance with 35 USC 112/2

The rejection was withdrawn by the Patent Office.

### 3. Compliance with 35 USC 112/1 enablement

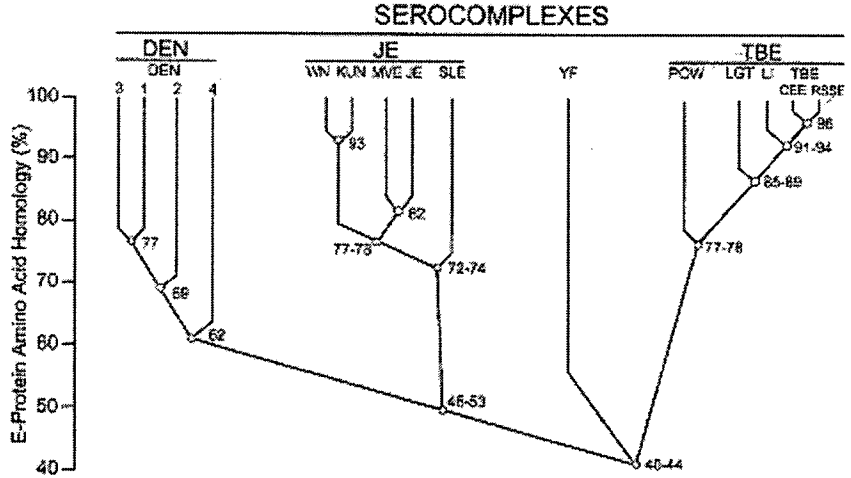
The rejection was withdrawn by the Patent Office.

### 4. Compliance with 35 USC 103(a)

The issue remains whether the claims are in compliance with 35 USC §103(a) or unpatentable over Westaway et al. (USP 6,893,866, see also WO 99/28487 of which the USP is a continuation application), in view of Schlesinger et al., J. Gen. Virol. 68: 853 (1987), Bartenschlager (USP 6,630,343), and Fields Virology 3rd ed., Philadelphia, Pa., Lippincott-Raven Publishers, pp. 931 et seq. (1996), and Claim 16 further in view of Khromykh & Westaway, J. Virol. 71: 1497 (1997).

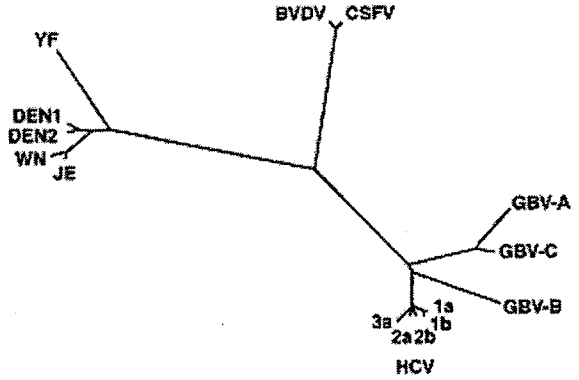
USP 6,893,866 describes construction of subgenomic replicons of Kunjin virus and their packaging into virus-like particles by a packaging cell line. Schlesinger et al. describes protection of mice against DEN 2 virus encephalitis by immunization with DEN 2 non-structural glycoprotein NS1. Bartenschlager is said to describe experiments with HCV. Varnavski & Khromykh, Virology 255: 366 (1999) and Khromykh & Westaway describe additional experiments with Kunjin. Behrens et al., J. Virol. 72: 2364 (1998) describes experiments with BVDV. Fields is said to teach that flaviviruses (of which dengue is a species) have structurally similar genomes.

Nevertheless, the construction of subgenomic replicons of Dengue virus and their packaging into virus-like particles could not have been predicted from USP 6,893,866 either singly or in combination with the other cited art. This is because, first, Kunjin belongs to the Japanese encephalitis virus group of flaviviruses whereas Dengue virus belongs to the different Dengue virus group.


SEROCOMPLEXES
DEN
JE
TBE
DEN
WN KUN MVE JE SLE
YF
POW LGT TBE
CEE RSSE
3 1 2 4
93
86
91-94
85-89
82
77
77-78
77-78
72-74
69
62
46-53
40-44
E-Protein Amino Acid Homology (%)
100
90
80
70
60
50
40

As shown in the art of Fields Virology 3rd ed., Philadelphia, Pa., Lippincott-Raven Publishers, pp. 931 et seq. (1996) at Fig. 2, above, the Japanese encephalitis virus group and Dengue viruses share only 46-53% amino acid sequence homologies as exemplified by E protein. Consequently, while flaviviruses share some common features with regard to genome organization, they share little sequence homology. Thus the construction of subgenomic replicons of Dengue virus and their packaging into virus-like particles could not have been predicted from the work with Kunjin virus.

Additionally, the construction of subgenomic replicons of Dengue virus and their packaging into virus-like particles could not have been predicted because, second, HCV and BVDV are not flaviviruses. Rather, they are members of the family Flaviviridae. HCV is not a flavivirus, instead it is a hepatitis C virus (Fields, Ref. 26, Table 1). BVDV is not a flavivirus, rather it is a pestivirus (Fields, Ref. 26, Table 1).


BVDV
CSFV
YF
DEN1
DEN2
WN
JE
GBV-A
GBV-C
GBV-B
1a
1b
3a
2a
2b
HCV

As shown in the art of Fields Virology 4th ed., Philadelphia, Pa., Lippincott Williams & Wilkins Publishers, pp. 991-1041 (2001) at Fig. 1, above, the three genera, the flaviviruses (of which Dengue virus is a member), the pestiviruses (of which BVDV is a member), and the hepaciviruses (of which HCV is a member), are phylogenetically diverse. Only Kunjin is a flavivirus, but as explained above, Kunjin belongs to the Japanese encephalitis virus group of flaviviruses whereas Dengue belongs to the different Dengue virus group. Thus the additional references do not assist in the construction of subgenomic replicons of Dengue virus and their packaging into virus-like particles.

At the time of the filing date, the development of flavivirus replicons had been investigated only for Kunjin. However, members of the flavivirus genus are quite diverse, as described above, and as evidenced by Khromykh et al. 1997, Ref. 14, on page 1504, col. 1, first paragraph, in which the authors report that a direct comparison between Kunjin and Dengue is difficult because of genetic heterogeneity. Therefore, the development of replicons from other flavivirus members, specifically dengue virus that demonstrates significant phylogenetic divergence, could not have been discerned in the absence of known properties common to the genus flavivirus from those specific to the particular member Kunjin.

In maintaining the rejection, the Patent Office took that position that Westaway et al. (WO99/28487) teaches the production of subgenomic replicons from "any flavivirus derived from any flavivirus RNA" and Kunjin as a preferred embodiment (p. 3, line 10; p. 6). MPEP 2144.08 provides guidelines for examining the obviousness of a species (here, subgenomic replicons of dengue virus) when the prior art teaches a genus. As it turns out, the prior art does not teach a genus, subsequently precluding the obviousness of the species dengue. Westaway et al. USP 6,893,866 issued on claims directed solely to the species subgenomic replicons of Kunjin virus and not to subgenomic replicons of flaviviruses as a class. In USP 6,893,866, Office Action dated 10/02/06, the Patent Office reasoned, under the rubric of unpredictability of the art, "While the flaviviruses share some common features with regard to genome organization, they share little sequence homology." The Patent Office argued that the state of the art was poorly developed, justifiably, because, despite the report of subgenomic replicons in the prior art for a number of non-flavi-plus-sense RNA viruses, and for BVDV and HCV of the family Flaviviridae, the generation of flavivirus replicons was the first report of its kind. The Patent Office posited, on the basis of the number of working examples, these taught only Kunjin virus.

The Patent Office took notice with regard to the scope of the claims that by reading on the more than 70 viruses of which the Flavivirus genus is composed, the claims were sweeping in their breadth. The Patent Office observed lack of guidance with respect to non-Kunjin viruses. The Patent Office evaluated the nature of the invention and made the point that the Kunjin virus was not a well-characterized member of the genus Flavivirus. Finally, the Patent Office concluded that, while the level of skill in the art was high, on balance, the Wands factors weighed against enablement by USP 6,893,866 of the claims directed to subgenomic replicons of flaviviruses as a class. Consequently, even the Patent Office agrees that USP 6,893,866, by describing Kunjin virus, does not teach the genus. Thus, under MPEP 2144.08, by not teaching the genus of subgenomic replicons of flaviviruses as a class, USP 6,893,866 cannot make obvious the species of subgenomic replicons of dengue virus.

In maintaining the 103 rejection, the Patent Office additionally made a case that Schlesinger 1987's finding of protection with NS1 would have provided motivation to substitute dengue virus for Kunjin in the Westaway work. Actually, the prior art would probably have prompted the field to turn in a different direction to subunit vaccines composed of NS1, not subgenomic replicons of dengue virus. Schlesinger 1987's finding was no reason for having led an immunologist to modify the Kunjin work to substitute dengue virus, when subunit vaccines were the usual alternative to inactivated or attenuated whole viruses as vaccines.

In maintaining the 103 rejection, the Patent Office further made a decision based on the cited art that there was a reasonable expectation of success. The substitution, however, of dengue virus for Kunjin in the Westaway work frustrates the intended purpose of the Westaway reference. This is because the heterologous genes were to be inserted into the 3' UTR of Kunjin virus. The latter approach presumably would not work for dengue virus. As noted by Khromykh & Westaway 1997, at paragraph bridging page 1503-1504, the differences in size of the 3' UTRs of dengue and Kunjin amounted to 624 nucleotides for Kunjin and only 384 nucleotides for dengue. The 3' UTR may be critical for dengue virus. In contrast, constructs with insertion of heterologous genes into the junction of the deleted structural region of dengue viruses were readily obtained (Specification at Example 2). Because of this frustration of the intended purpose, MPEP 2143.01 says the invention is nonobvious.

For these reasons, the conclusion is the claims are patentable over any prior art and in compliance with 35 U.S.C. §103(a).

**5. Compliance with Rules Against Double Patenting**

The Patent Office provisionally rejected certain of the pending claims under the judicially created doctrine of obviousness-type double patenting as being unpatentable over selected claims of U.S. Pat. Appl. No. 11/192,923, filed July 29, 2005, or U.S. Pat. Appl. No. 11/194,342, filed still later based on its Serial No. The rule according to MPEP 804 I B 1 is that if a "provisional" obviousness-type double patenting rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer. Where there are three applications containing claims that conflict such that an obviousness-type double patenting rejection is made in each application based upon the other two, it is not sufficient to file a terminal disclaimer in only one of the applications addressing the other two applications. Rather, an appropriate terminal disclaimer must be filed in at least two of the applications to link all three together. Here, a "provisional" obviousness-type double patenting rejection is the only rejection remaining in the earliest filed of all three pending applications, because this application was filed September 5, 2003, while U.S. Pat. Appl. No. 11/192,923 was filed July 29, 2005 and U.S. Pat. Appl. No. 11/194,342 was filed even later based on its Serial No. Consequently, an appropriate terminal disclaimer can be filed in the two later-filed applications to link all three together if an obviousness-type double patenting rejection remains in the two later-filed applications. Thus, the examiner is respectfully requested to withdraw the rejection in this application and permit the earliest-filed application to issue as a patent without a terminal disclaimer.

## CONCLUSION

Applicant respectfully requests that a timely Notice of Allowance be issued in this case. If any points remain that can be resolved by telephone, the Examiner is invited to contact the undersigned at the below-given telephone number.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 7/9/07

By: _____

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AMEND

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